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(54) Title: UROTENSIN-II RECEPTOR ANTAGONISTS

(57) Abstract: The present invention relates to pyrrolidines, pharmaceutical compositions containing them and their use as antago-
nists of urotensin II.

UROTENSIN-II RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates generally to pyrrolidines, pharmaceutical
5 compositions containing them, and their use as antagonists of urotensin II.

BACKGROUND OF THE INVENTION

The integrated control of cardiovascular homeostasis is achieved through a combination of both direct neuronal control and systemic neurohormonal activation.
10 Although the resultant release of both contractile and relaxant factors is normally under stringent regulation, an aberration in this *status quo* can result in cardiohemodynamic dysfunction with pathological consequences.

The principal mammalian vasoactive factors that comprise this neurohumoral axis, namely angiotensin-II, endothelin-1, norepinephrine, all function via an interaction with
15 specific G-protein coupled receptors (GPCR). Urotensin-II, represents a novel member of this neurohumoral axis.

In the fish, this peptide has significant hemodynamic and endocrine actions in diverse end-organ systems and tissues:

- smooth muscle contraction
20 both vascular and non-vascular in origin including smooth muscle preparations from the gastrointestinal tract and genitourinary tract. Both pressor and depressor activity has been described upon systemic administration of exogenous peptide
- osmoregulation:
effects which include the modulation of transepithelial ion (Na^+ , Cl^-) transport.
25 Although a diuretic effect has been described, such an effect is postulated to be secondary to direct renovascular effects (elevated GFR)
- metabolism:
urotensin-II influences prolactin secretion and exhibits a lipolytic effect in fish (activating triacylglycerol lipase resulting in the mobilization of non-esterified free
30 fatty acids)
(Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* **1980**, 77, 5021; Conlon, *et. al. J. Exp. Zool.* **1996**, 275, 226.)

In studies with human Urotensin-II it was found that it:

- was an extremely potent and efficacious vasoconstrictor
- 35 • exhibited sustained contractile activity that was extremely resistant to wash out

- exhibited sustained contractile activity that was extremely resistant to wash out
- had detrimental effects on cardiac performance (myocardial contractility)

Human Urotensin-II was assessed for contractile activity in the rat-isolated aorta and was shown to be the most potent contractile agonist identified to date. Based on the *in vitro* pharmacology and *in vivo* hemodynamic profile of human Urotensin-II it plays a pathological role in cardiovascular diseases characterized by excessive or abnormal vasoconstriction and myocardial dysfunction. (Ames *et. al. Nature* **1999**, *401*, 282) Compounds that antagonize the Urotensin-II receptor may be useful in the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, restenosis, asthma, (Hay DWP, Luttmann MA, Douglas SA: 2000, Br J Pharmacol: In press.) neurogenic inflammation and metabolic vasculopathies all of which are characterized by abnormal vasoconstriction and/or myocardial dysfunction. Since U-II and GPR14 are both expressed within the mammalian CNS (Ames *et. al. Nature* **1999**, *401*, 282), they also may be useful in the treatment of addiction, schizophrenia, impulsivity, anxiety, stress, depression, and neuromuscular function. Functional U-II receptors are expressed in rhabdomyosarcomas cell lines and therefore may have oncological indications. Urotensin may also be implicated in various metabolic diseases such as diabetes (Ames *et. al. Nature* **1999**, *401*, 282, Nothacker *et al.*, *Nature Cell Biology* **1**: 383-385, 1999)

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SUMMARY OF THE INVENTION

In one aspect this invention provides for pyrrolidines and pharmaceutical compositions containing them.

In a second aspect, this invention provides for the use of pyrrolidines as antagonists of urotensin II, and as inhibitors of urotensin II.

25

In another aspect, this invention provides for the use of pyrrolidines for treating conditions associated with urotensin II imbalance.

In an yet another aspect, this invention provides for the use of these pyrrolidine analogs for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, restenosis, asthma, neurogenic inflammation and metabolic vasculopathies, addiction, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function, and diabetes.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors,

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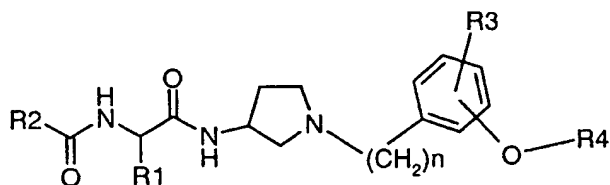
vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β -adrenoceptor and α_1 -adrenoceptor antagonists.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

5

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula I:



Formula (I)

10

wherein:

R1 is isobutyl, isopropyl, benzyl, carbamoylmethyl;

R2 is methyl, phenyl, naphthyl, indolyl, benzimidazolyl, quinolinyl, furanyl, thiophenyl,

15 pyridyl, benzofuranyl, or benzothiophenyl, substituted or unsubstituted by one or two halogen, methyl, methoxy, or methylenedioxy groups;

R3 is hydrogen, halogen, methyl, methoxy, nitro, or 2,3-(1,3-butadien-1,4-yl);

R4 is 3-dimethylaminopropyl, 2-(pyrrolidin-1-yl)ethyl, 2-(1-morpholino)ethyl, 2-(N-methyl anilino)ethyl, 2-(1-piperazinyl)ethyl, 2-(1-pyrrolidinonyl)ethyl, (1-methylpyrrolidin-2(S)-

20 yl)methyl, 1-methylpyrrolidin-3(\pm)-yl, 1-benzylpiperidin-4-yl, (6-methylpyrid-2-yl)methyl, 3-dimethylamino benzyl, 2(S)-(aminocarbonyl) pyrrolidin-4(S)-yl, pyrrolidin-3(S)-yl, piperidin-4-yl, pyrrolidin-3(R)-yl, or *cis*-4-aminocyclohexyl; and

n is 1 or 2;

or a pharmacologically acceptable salt thereof.

25

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

30

R1 is preferably isobutyl, isopropyl, or benzyl.

R₂ preferably is phenyl, naphthyl, furanyl, thiophenyl, benzofuranyl, or benzothiophenyl, substituted or unsubstituted with one or two halogen, methyl, methoxy, or methylenedioxy groups.

R₃ preferably is hydrogen, halogen, methyl, or methoxy.

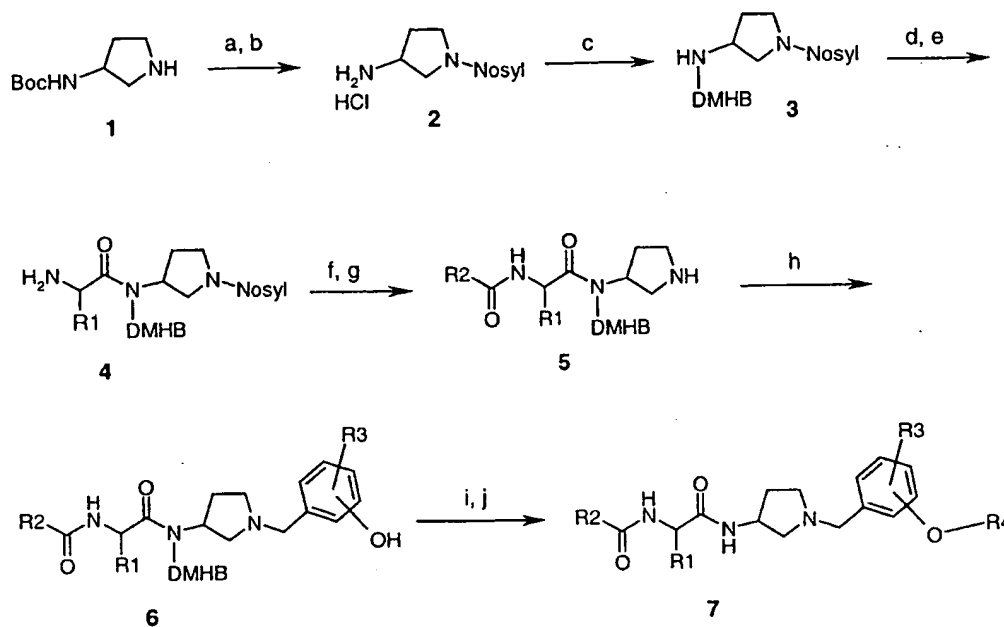
- 5 R₄ is preferably 3-dimethylaminopropyl, 2-(1-piperazinyl)ethyl, 2-(1-pyrrolidinonyl) ethyl, 1-methylpyrrolidin-3(±)-yl, 1-benzylpiperidin-4-yl, pyrrolidin-3(S)-yl, piperidin-4-yl, or pyrrolidin-3(R)-yl.

Preferred Compounds are:

- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-iodo-3-(2-piperazin-1-yl-ethoxy)-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide;
- 10 Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[3-(3-dimethylamino-propoxy)-4-iodo-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide;
- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-(3-dimethylamino-propoxy)-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide;
- 15 Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-(1-benzyl-piperidin-4-yloxy)-3-chloro-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide;
- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[3-bromo-4-(3-dimethylamino-propoxy)-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide;
- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[3-bromo-4-(1-methyl-pyrrolidin-3-yloxy)-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide;
- 20 Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-(1-benzyl-piperidin-4-yloxy)-3-bromo-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide;
- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-(3-dimethylamino-propoxy)-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide;
- 25 Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[3-bromo-4-(piperidin-4-yloxy)-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide; and
- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[3-bromo-4-((R)-pyrrolidin-3-yloxy)-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide.

Compounds of Formula (I) may be prepared as outlined in the following schemes:

Scheme 1



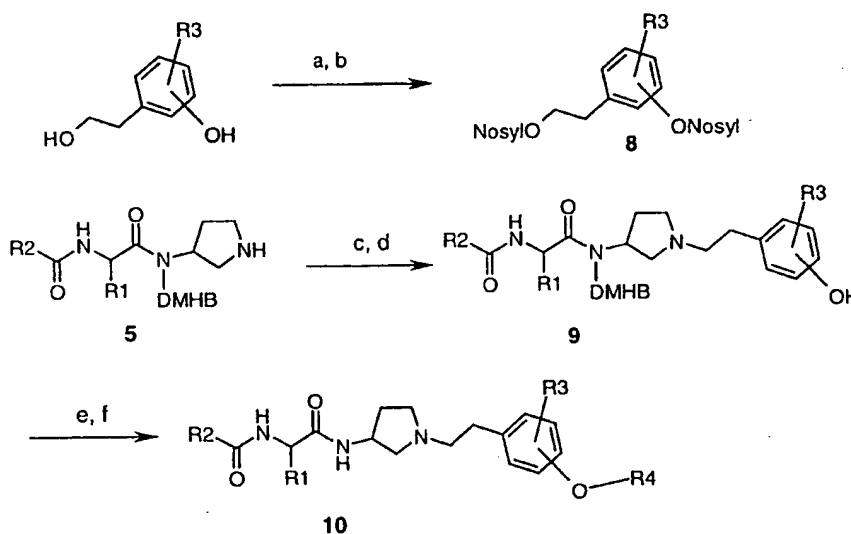
- 5 Conditions: a) 2-nitrobenzenesulfonyl chloride, pyridine, CH_2Cl_2 , 0°C – rt; b) 4 M HCl
in 1,4-dioxane, MeOH, rt; c) 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB
resin), $\text{Na}(\text{OAc})_3\text{BH}$, diisopropylethylamine, 1% acetic acid in 1-methyl-2-pyrrolidinone, rt;
d) Fmoc-HNCH(R_1)COOH, 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-
methyl-2-pyrrolidinone, rt; e) 20% piperidine in 1-methyl-2-pyrrolidinone, rt; f) R_2COOH ,
10 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-methyl-2-pyrrolidinone, rt;
g) K_2CO_3 , PhSH, 1-methyl-2-pyrrolidinone, rt; h) $(\text{R}_3)(\text{OH})\text{PhCHO}$, $\text{Na}(\text{OAc})_3\text{BH}$, 10%
acetic acid in 1-methyl-2-pyrrolidinone, rt; i) R_4OH , diisopropyl azodicarboxylate, PPh_3 ,
tetrahydrofuran, -78°C – rt; j) 50% trifluoroacetic acid in 1,2-dichloroethane, rt. (R_1 , R_2 ,
 R_3 and R_4 are as defined above.)

15

Resin-bound amine **3** was prepared by reductive amination of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) with N-nosylated diamine hydrochloride salt **2** which was prepared from 3(*S*)-(-)-(*tert*-butoxycarbonyl-amino)pyrrolidine (**1**) (Scheme 1). Reactions of resin-bound amine **3** with various amino acids, followed by removal of the protecting group, provided resin-bound amines **4**. Amines **4** were then reacted with various acids to afford the corresponding resin-bound amides

- which were subsequently treated with potassium carbonate and thiophenol to give secondary amines **5**. Reductive amination of resin-bound amines **5** with various hydroxy benzaldehydes produced resin-bound phenols **6**. Phenols **6** were then reacted with various alcohols in the presence of triphenylphosphine and diisopropyl azodicarboxylate to give the corresponding resin-bound phenol ethers which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targetted compounds **7**.

Scheme 2:



10

Conditions: a) 2-nitrobenzenesulfonyl chloride, sodium hydride, tetrahydrofuran, rt; b) ether, water, 0 °C; c) bis-nosylates **8**, tetrabutylammonium iodide, 1-methyl-2-pyrrolidinone, rt to 65 °C; d) potassium trimethylsilanolate, tetrahydrofuran, rt; e) R₄OH, diisopropyl azodicarboxylate, PPh₃, tetrahydrofuran, - 78 °C – rt; f) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

15

As shown in scheme 2, bis-nosylates **8** were synthesized from various commercially available or known hydroxyphenethyl alcohols. Phenols **9** were prepared by reactions of previously synthesized amines **5** (scheme 1) with bis-nosylates **8** in the presence of tetrabutylammonium iodide, followed by hydrolysis of the resulting mononosylate intermediates. Phenols **9** were then reacted with various alcohols in the presence of triphenylphosphine and diisopropyl azodicarboxylate to give the corresponding resin-bound phenol ethers which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targetted compounds **10**.

20

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

These pyrrolidine analogs may be used for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, restenosis, asthma, neurogenic inflammation and metabolic vasculopathies, addiction, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function, and diabetes.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β -adrenoceptor and α_1 -adrenoceptor antagonists.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

Radioligand binding:

HEK-293 cell membranes containing stable cloned human and rat GPR-14 (20 ug/assay) were incubated with 200 pM [¹²⁵I] h-U-II (200 Ci/mmol¹ in the presence of increasing concentrations of test compounds in DMSO (0.1 nM to 10 uM), in a final incubation volume of 200 ul (20 mM Tris-HCl, 5 mM MgCl₂). Incubation was done for 30 minutes at room temperature followed by filtration GF/B filters with Brandel cell harvester. ¹²⁵I labeled U-II binding was quantitated by gamma counting. Nonspecific binding was defined by ¹²⁵I U-II binding in the presence of 100 nM of unlabeled human U-II. Analysis of the data was performed by nonlinear least square fitting.

10

Ca²⁺-mobilization:

A microtitre plate based Ca²⁺-mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA) was used for the functional identification of the ligand activating HEK-293 cells expressing (stable) recombinant GPR-14. The day following transfection, cells were plated in a poly-D-lysine coated 96 well black/clear plates. After 18-24 hours the media was aspirated and Fluo 3AM-loaded cells were exposed to various concentrations (10 nM to 30 uM) of test compounds followed by h-U-II. After initiation of the assay, fluorescence was read every second for one minute and then every 3 seconds for the following one minute. The inhibitory concentration at 50% (IC₅₀) was calculated for various test compounds.

20

Inositol phosphates assays:

HEK-293-GPR14 cells in T150 flask were prelabeled overnight with 1 uCi myo-[³H] inositol per ml of inositol free Dulbecco's modified Eagle's medium. After labeling, the cells were washed twice with Dulbecco's phosphate-buffered saline (DPBS) and then incubated in DPBS containing 10 mM LiCl for 10 min at 37°C. The experiment was initiated by the addition of increasing concentrations of h-U-II (1 pM to 1 μM) in the absence and presence of three different concentrations (0.3, 1 and 10 uM) of test compounds and the incubation continued for an additional 5 min at 37°C after which the reaction was terminated by the addition of 10% (final concentration) trichloroacetic acid and centrifugation. The supernatants were neutralized with 100ul of 1M Trizma base and the inositol phosphates were separated on AG 1-X8 columns (0.8 ml packed, 100-200 mesh) in formate phase. Inositol monophosphate was eluted with 8 ml of 200 mM ammonium formate. Combined inositol di and tris phosphate was eluted with 4ml of 1M ammonium

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formate/ 0.1 M formic acid. Eluted fractions were counted in beta scintillation counter.

Based on shift from the control curve K_B was calculated.

Activity for the compounds of this invention range from (radioligand binding assay): $K_i = 1 \text{ nM} - 10000 \text{ nM}$ (example 15 $K_i = 390 \text{ nM}$)

5

Example 1

Preparation of Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-(3-dimethylamino-propoxy)-benzyl]-pyrrolidin-3-ylcarbonyl)-3-methyl-butyl)-amide

10 a) 3(S)-amino-N-(2-nitrobenzenesulfonyl)pyrrolidine HCl salt

To a solution of 3(S)-(-)-(tert-butoxycarbonyl-amino)pyrrolidine (20.12 g, 108 mmol) in 250 mL of anhydrous methylene chloride at 0 °C was added 13.1 mL (162 mmol) of anhydrous pyridine, followed by slow addition of 25.2 g (113.4 mmol) of 2-nitrobenzenesulfonyl chloride. The mixture was warmed to rt over 1 h and was stirred at rt for 16 h. The mixture was poured into 300 mL of 1 M aqueous NaHCO_3 solution. After the resulting mixture was stirred at rt for 30 min, the organic layer was separated and was washed with 500 mL of 1N aqueous HCl solution twice. The resulting organic layer was dried over MgSO_4 and concentrated *in vacuo*. The residue was used for the the next step without further purification.

20 To a mixture of the above residue in 140 mL of anhydrous MeOH was added 136 mL (544 mmol) of 4 M HCl in 1,4-dioxane solution. The mixture was stirred at rt for 16 h, concentrated *in vacuo* and further dried in vacuum oven at 35 °C for 24 h to yield 3(S)-amino-N-(2-nitrobenzenesulfonyl) pyrrolidine HCl salt as a yellow solid (30.5 g, 92% over the two steps): ^1H NMR (400 MHz, d_6 -DMSO) δ 8.63 (s, 3 H), 8.08-7.98 (m, 2 H), 7.96-7.83 (m, 2 H), 3.88-3.77 (m, 1 H), 3.66-3.56 (m, 2 H), 3.46-3.35 (m, 2 H), 2.28-2.16 (m, 1 H), 2.07-1.96 (m, 1 H).

30 b) benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-(3-dimethylamino-propoxy)-benzyl]-pyrrolidin-3-ylcarbonyl)-3-methyl-butyl)-amide

To a mixture of 7.20 g (10.37 mmol, 1.44 mmol/g) of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) in 156 mL of 1% acetic acid in anhydrous 1-methyl-2-pyrrolidinone was added 9.56 g (31.1 mmol) of example 1a and 9.03 mL (51.84 mmol) of diisopropylethyl amine, followed by addition of 11.0 g (51.84 mmol) of sodium triacetoxymethylborohydride. After the resulting mixture was shaken at rt for 72 h, the

resin was washed with DMF (3 x 250 mL), CH₂Cl₂/MeOH (1:1, 3 x 250 mL) and MeOH (3 x 250 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. Elemental analysis N: 4.16, S: 3.12.

To a mixture of 800 mg (0.860 mmol, 1.075 mmol/g) of the above resin in 15 mL of anhydrous 1-methyl-2-pyrrolidinone was added 1.52 g (4.30 mmol) of Fmoc-Leu-OH and 117 mg (0.86 mmol) of 1-hydroxy-7-azabenzotriazole, followed by addition of 0.82 mL (5.16 mmol) of 1,3-diisopropylcarbodiimide. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 25 mL), CH₂Cl₂/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 607 [M+H]⁺.

The above resin (0.860 mmol) was treated with 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution. After the mixture was shaken at rt for 15 min, the solution was drained and another 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution was added. The mixture was shaken at rt for another 15 min. The solution was drained and the resin was washed with DMF (3 x 25 mL), CH₂Cl₂/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 385 [M+H]⁺.

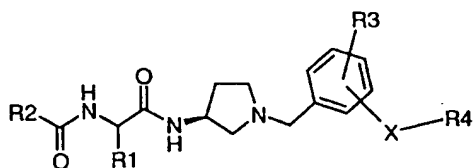
To a mixture of 200 mg (0.1918 mmol, 0.959 mmol/g) of the above dry resin in 5 mL of anhydrous 1-methyl-2-pyrrolidinone was added 267.3 mg (1.50 mmol) of benzo[b]thiophene-2-carboxylic acid and 41 mg (0.30 mmol) of 1-hydroxy-7-azabenzotriazole, followed by addition of 0.28 mL (1.80 mmol) of 1,3-diisopropylcarbodiimide. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 545 [M+H]⁺.

To a mixture of the above dry resin (0.1918 mmol) in 6.4 mL of 1-methyl-2-pyrrolidinone was added 265 mg (1.918 mmol) of K₂CO₃ and 0.0985 mL (0.96 mmol) of PhSH. After the resulting mixture was shaken at rt for 2 h, the resin was washed with DMF (3 x 10 mL), H₂O (3 x 10 mL), DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and

MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 719 [2M+H]⁺, 360 [M+H]⁺.

- 5 To a mixture of the above dry resin (0.1918 mmol) in 6.4 mL of 10% HOAc in anhydrous 1-methyl-2-pyrrolidinone solution was added 234 mg (1.918 mmol) of 4-hydroxybenzaldehyde and 407 mg (1.918 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 72 h, the resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was
- 10 dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 466 [M+H]⁺.

- To a mixture of the above dry resin (0.1918 mmol) in 10.7 mL of anhydrous tetrahydrofuran was added 227 mg (1.918 mmol) of 3-dimethylaminopropanol and 503 mg
- 15 (1.918 mmol) of triphenylphosphine. After the mixture was cooled to -78 °C, 378 mg (1.918 mmol) of diisopropyl azodicarboxylate was added to the cold mixture. The resulting mixture was kept at -70 °C for 30 min while shaking. The mixture was then allowed to warm to 0 °C over 1 h and shaken at rt for 16 h. The resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was
- 20 dried in vacuum oven at 35 °C for 24 h. The dry resin was treated with 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column
- 25 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H₂O (0.1% trifluoroacetic acid) and B = CH₃CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-(3-dimethylamino-propoxy)-benzyl]-pyrrolidin-3-ylcarbonyl)-3-methyl-butyl)-amide as a bis-trifluoroacetic acid salt (white powder, 101 mg, 68% over 7 steps): MS (ESI) 551
- 30 [M+H]⁺.



Compounds derived from Scheme 1:

Example	R1	R2	X	R3	R4	MS (ES+) m/e
2	(S)-isobutyl	2-naphthyl	4-oxy	H	3-dimethyl aminopropyl	545 (M+H)
3	(S)-isobutyl	phenyl	4-oxy	H	3-dimethyl aminopropyl	495 (M+H)
4	(S)-isobutyl	5-benzimidazolyl	4-oxy	H	3-dimethyl aminopropyl	535 (M+H)
5	(S)-isobutyl	2-indolyl	4-oxy	H	3-dimethyl aminopropyl	534 (M+H)
6	(S)-isobutyl	3,4-methylene dioxypheyl	4-oxy	H	3-dimethyl aminopropyl	539 (M+H)
7	(S)-isobutyl	benzofuran-2-yl	4-oxy	H	3-dimethyl aminopropyl	535 (M+H)
8	(S)-isobutyl	2-quinoliny	4-oxy	H	3-dimethyl aminopropyl	546 (M+H)
9	(S)- isopropyl	3,4-dichloro phenyl	4-oxy	H	3-dimethyl aminopropyl	549 (M+H)
10	(S)- isopropyl	4-bromophenyl	4-oxy	H	3-dimethyl aminopropyl	559 (M+H)
11	(S)- isopropyl	2-furanyl	4-oxy	H	3-dimethyl aminopropyl	471 (M+H)
12	(S)- isopropyl	3,4-methylene dioxymethyl	4-oxy	H	3-dimethyl aminopropyl	539 (M+H)
13	(S)-benzyl	phenyl	4-oxy	H	3-dimethyl aminopropyl	529 (M+H)
14	(S)-benzyl	3,4-dichloro phenyl	4-oxy	H	3-dimethyl aminopropyl	597 (M+H)
15	(S)-benzyl	4-bromophenyl	4-oxy	H	3-dimethyl aminopropyl	607 (M+H)
16	(S)-benzyl	benzofuran-2-yl	4-oxy	H	3-dimethyl aminopropyl	569 (M+H)
17	(S)-benzyl	4,5-dimethyl	4-oxy	H	3-dimethyl aminopropyl	547

		furan-2-yl				(M+H)
18	(S)-benzyl	3,4-methylene dioxymethyl	4-oxy	H	3-dimethyl aminopropyl	587 (M+H)
19	(S)-carbamoylmethyl	4-bromophenyl	4-oxy	H	3-dimethyl aminopropyl	574 (M+H)
20	(S)-carbamoylmethyl	benzofuran-2-yl	4-oxy	H	3-dimethyl aminopropyl	536 (M+H)
21	(S)-isobutyl	3,4-dichlorophenyl	4-oxy	H	3-dimethyl aminopropyl	563 (M+H)
22	(S)-isobutyl	4-bromophenyl	4-oxy	H	3-dimethyl aminopropyl	573 (M+H)
23	(S)-isobutyl	2-furanyl	4-oxy	H	3-dimethyl aminopropyl	485 (M+H)
24	(S)-isobutyl	6-methyl-2-pyridyl	4-oxy	H	3-dimethyl aminopropyl	510 (M+H)
25	(S)-isobutyl	thiophene-2-yl	4-oxy	H	3-dimethyl aminopropyl	501 (M+H)
26	(S)-isobutyl	3,4-methylene dioxymethyl	4-oxy	H	3-dimethyl aminopropyl	539 (M+H)
27	(S)-isobutyl	methyl	4-oxy	H	3-dimethyl aminopropyl	433 (M+H)
28	(S)-isobutyl	4,5-dimethyl-2-furanyl	4-oxy	H	3-dimethyl aminopropyl	513 (M+H)
29	(S)-isobutyl	4-pyridyl	4-oxy	H	3-dimethyl aminopropyl	496 (M+H)
30	(S)-isobutyl	3,4-methylene dioxymethyl	4-oxy	H	3-dimethyl aminopropyl	553 (M+H)
31	(R)-isobutyl	3,4-dichlorophenyl	4-oxy	H	3-dimethyl aminopropyl	563 (M+H)
32	(R)-isobutyl	4-bromophenyl	4-oxy	H	3-dimethyl aminopropyl	573 (M+H)
33	(R)-isobutyl	benzofuran-2-yl	4-oxy	H	3-dimethyl aminopropyl	535 (M+H)
34	(S)-isobutyl	benzo[b]thiophene-2-yl	3-oxy	H	3-dimethyl aminopropyl	551 (M+H)
35	(S)-isobutyl	benzo[b]thiophene-2-yl	3-oxy	4-iodo	3-dimethyl aminopropyl	677 (M+H)
36	(S)-isobutyl	benzo[b]thiophene-2-yl	4-oxy	2,3-(1,3-butadien-1,4-yl)	3-dimethyl aminopropyl	601 (M+H)

37	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2- methoxy	3-dimethyl aminopropyl	581 (M+H)
38	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-methyl	3-dimethyl aminopropyl	565 (M+H)
39	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-bromo	3-dimethyl aminopropyl	629 (M+H)
40	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	H	2-(pyrrolidin-1-yl) ethyl	563 (M+H)
41	(S)-isobutyl	benzo[b]thiophene -2-yl	3-oxy	4-iodo	2-(pyrrolidin-1-yl) ethyl	689 (M+H)
42	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2- methoxy	2-(pyrrolidin-1-yl) ethyl	593 (M+H)
43	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-methyl	2-(pyrrolidin-1-yl) ethyl	577 (M+H)
44	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-bromo	2-(pyrrolidin-1-yl) ethyl	641 (M+H)
45	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	H	2-(1-morpholino) ethyl	579 (M+H)
46	(S)-isobutyl	benzo[b]thiophene -2-yl	3-oxy	4-iodo	2-(1-morpholino) ethyl	705 (M+H)
47	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-methyl	2-(1-morpholino) ethyl	593 (M+H)
48	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-bromo	2-(1-morpholino) ethyl	657 (M+H)
49	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2,3-(1,3- butadien- 1,4-yl)	2-(N-methyl anilino)ethyl	649 (M+H)
50	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2- methoxy	2-(N-methyl anilino)ethyl	629 (M+H)
51	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-methyl	2-(N-methyl anilino)ethyl	613 (M+H)
52	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	H	2-(1-piperazinyl) ethyl	578 (M+H)
53	(S)-isobutyl	benzo[b]thiophene -2-yl	3-oxy	H	2-(1-piperazinyl) ethyl	578 (M+H)
54	(S)-isobutyl	benzo[b]thiophene -2-yl	3-oxy	4-iodo	2-(1-piperazinyl) ethyl	704 (M+H)
55	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2,3-(1,3- butadien- 1,4-yl)	2-(1-piperazinyl) ethyl	628 (M+H)
56	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2- methoxy	2-(1-piperazinyl) ethyl	608 (M+H)

57	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-chloro	2-(1-piperazinyl) ethyl	612 (M+H)
58	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-methyl	2-(1-piperazinyl) ethyl	592 (M+H)
59	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-bromo	2-(1-piperazinyl) ethyl	656 (M+H)
60	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2,3-(1,3- butadien- 1,4-yl)	2-(1-pyrrolidinonyl) ethyl	627 (M+H)
61	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-methyl	2-(1-pyrrolidinonyl) ethyl	591 (M+H)
62	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	H	(1-methyl pyrrolidin- 2(S)-yl)methyl	563 (M+H)
63	(S)-isobutyl	benzo[b]thiophene -2-yl	3-oxy	H	(1-methyl pyrrolidin- 2(S)-yl)methyl	563 (M+H)
64	(S)-isobutyl	benzo[b]thiophene -2-yl	3-oxy	4-iodo	(1-methyl pyrrolidin- 2(S)-yl)methyl	689 (M+H)
65	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2,3-(1,3- butadien- 1,4-yl)	(1-methyl pyrrolidin- 2(S)-yl)methyl	613 (M+H)
66	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2- methoxy	(1-methyl pyrrolidin- 2(S)-yl)methyl	593 (M+H)
67	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-chloro	(1-methyl pyrrolidin- 2(S)-yl)methyl	597 (M+H)
68	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-methyl	(1-methyl pyrrolidin- 2(S)-yl)methyl	577 (M+H)
69	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-bromo	(1-methyl pyrrolidin- 2(S)-yl)methyl	641 (M+H)
70	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	H	1-methyl pyrrolidin- 3(±)-yl	549 (M+H)
71	(S)-isobutyl	benzo[b]thiophene -2-yl	3-oxy	H	1-methyl pyrrolidin- 3(±)-yl	549 (M+H)
72	(S)-isobutyl	benzo[b]thiophene -2-yl	3-oxy	4-iodo	1-methyl pyrrolidin- 3(±)-yl	675 (M+H)
73	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2,3-(1,3- butadien- 1,4-yl)	1-methyl pyrrolidin- 3(±)-yl	599 (M+H)
74	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2- methoxy	1-methyl pyrrolidin- 3(±)-yl	579 (M+H)
75	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-chloro	1-methyl pyrrolidin- 3(±)-yl	583 (M+H)
76	(S)-isobutyl	benzo[b]thiophene	4-oxy	3-methyl	1-methyl pyrrolidin-	563

		-2-yl			3(±)-yl	(M+H)
77	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-bromo	1-methyl pyrrolidin- 3(±)-yl	627 (M+H)
78	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	H	1-benzyl piperidin-4-yl	639 (M+H)
79	(S)-isobutyl	benzo[b]thiophene -2-yl	3-oxy	4-iodo	1-benzyl piperidin-4-yl	765 (M+H)
80	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2- methoxy	1-benzyl piperidin-4-yl	669 (M+H)
81	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-chloro	1-benzyl piperidin-4-yl	673 (M+H)
82	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-methyl	1-benzyl piperidin-4-yl	653 (M+H)
83	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-bromo	1-benzyl piperidin-4-yl	717 (M+H)
84	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	H	(6-methylpyrid-2- yl)methyl	571 (M+H)
85	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	H	3-dimethylamino benzyl	599 (M+H)
86	(S)-isobutyl	benzo[b]thiophene -2-yl	3-oxy	4-iodo	3-dimethylamino benzyl	725 (M+H)
87	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2,3-(1,3- butadien- 1,4-yl)	3-dimethylamino benzyl	649 (M+H)
88	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-chloro	3-dimethylamino benzyl	633 (M+H)
89	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	H	2(S)-(aminocarbonyl) pyrrolidin-4(S)-yl	578 (M+H)
90	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	2,3-(1,3- butadien- 1,4-yl)	2(S)-(aminocarbonyl) pyrrolidin-4(S)-yl	628 (M+H)
91	(S)-isobutyl	benzo[b]thiophene- 2-yl	4-oxy	2- methoxy	2(S)-(aminocarbonyl) pyrrolidin-4(S)-yl	608 (M+H)
92	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-chloro	2(S)-(aminocarbonyl) pyrrolidin-4(S)-yl	612 (M+H)
93	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-bromo	2(S)-(aminocarbonyl) pyrrolidin-4(S)-yl	656 (M+H)
94	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-bromo	piperidin-4-yl	627 (M+H)
95	(S)-isobutyl	benzo[b]thiophene -2-yl	4-oxy	3-bromo	pyrrolidin-3(R)-yl	613 (M+H)

Example 96Preparation of Benzo[b]thiophene-2-carboxylic acid [(S)-3-methyl-1-((S)-1-{2-[4-((S)-pyrrolidin-3-yloxy)-phenyl]-ethyl}-pyrrolidin-3-ylcarbamoyl)-butyl]-amide

- 5 a) 2-nitrobenzenesulfonic acid 2-[4-(2-nitrobenzenesulfonyloxy)-phenyl]-ethyl ester

To a mixture of 2.76 g (20 mmol) of 4-hydroxyphenethyl alcohol in 70 mL of anhydrous tetrahydrofuran at rt was added 4.8 g (200 mmol) of sodium hydride (95%, dry powder). After stirring at rt for 10 min, 18.5 g (80 mmol) of 2-nitrobenzenesulfonyl chloride was added. After the resulting mixture was stirred at rt for 16 h, 250 mL of ether
 10 was added. The mixture was cooled to 0 °C and water was slowly added to the mixture to quench excess sodium hydride. After quenching process was completed, additional 300 mL of water was added. The resulting precipitate was collected via filtration, washed with water and dried *in vacuo* to yield 2-nitrobenzenesulfonic acid 2-[4-(2-nitrobenzenesulfonyloxy)-phenyl]-ethyl ester as a white powder (9.13 g, 90%): MS (ESI)
 15 509 [M+H]⁺.

- b) benzo[b]thiophene-2-carboxylic acid [(S)-3-methyl-1-((S)-1-{2-[4-((S)-pyrrolidin-3-yloxy)-phenyl]-ethyl}-pyrrolidin-3-ylcarbamoyl)-butyl]-amide

To a mixture of 7.20 g (10.37 mmol, 1.44 mmol/g) of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) in 156 mL of 1% acetic acid in
 20 anhydrous 1-methyl-2-pyrrolidinone was added 9.56 g (31.1 mmol) of example 1a and 9.03 mL (51.84 mmol) of diisopropylethyl amine, followed by addition of 11.0 g (51.84 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 72 h, the resin was washed with DMF (3 x 250 mL), CH₂Cl₂/MeOH (1:1, 3 x 250 mL) and MeOH (3
 25 x 250 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. Elemental analysis N: 4.16, S: 3.12.

To a mixture of 800 mg (0.860 mmol, 1.075 mmol/g) of the above resin in 15 mL of anhydrous 1-methyl-2-pyrrolidinone was added 1.52 g (4.30 mmol) of Fmoc-Leu-OH and 117 mg (0.86 mmol) of 1-hydroxy-7-azabenzotriazole, followed by addition of 0.82 mL
 30 (5.16 mmol) of 1,3-diisopropylcarbodiimide. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 25 mL), CH₂Cl₂/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 607 [M+H]⁺.

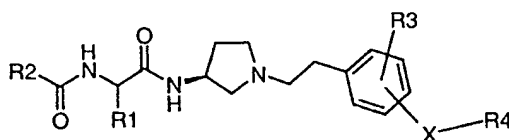
- The above resin (0.860 mmol) was treated with 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution. After the mixture was shaken at rt for 15 min, the solution was drained and another 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution was added. The mixture was shaken at rt for another 15 min. The solution was drained and the resin was washed with DMF (3 x 25 mL), CH₂Cl₂/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 385 [M+H]⁺.
- To a mixture of 200 mg (0.1918 mmol, 0.959 mmol/g) of the above dry resin in 5 mL of anhydrous 1-methyl-2-pyrrolidinone was added 267.3 mg (1.50 mmol) of benzo[b]thiophene-2-carboxylic acid and 41 mg (0.30 mmol) of 1-hydroxy-7-azabenzotriazole, followed by addition of 0.28 mL (1.80 mmol) of 1,3-diisopropylcarbodiimide. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 545 [M+H]⁺.
- To a mixture of the above dry resin (0.1918 mmol) in 6.4 mL of 1-methyl-2-pyrrolidinone was added 265 mg (1.918 mmol) of K₂CO₃ and 0.0985 mL (0.96 mmol) of PhSH. After the resulting mixture was shaken at rt for 2 h, the resin was washed with DMF (3 x 10 mL), H₂O (3 x 10 mL), DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 719 [2M+H]⁺, 360 [M+H]⁺.
- To a mixture of the above dry resin (0.1918 mmol) in 6.4 mL of anhydrous 1-methyl-2-pyrrolidinone solution was added 468 mg (0.959 mmol) of 2-nitrobenzenesulfonic acid 2-[4-(2-nitrobenzenesulfonyloxy)-phenyl]-ethyl ester and 708 mg (1.918 mmol) of tetrabutylammonium iodide. After the resulting mixture was shaken at rt for 8 days and subsequently at 65 °C for 20 h, the resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and THF (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50%

trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 665 [M+H]⁺.

To a mixture of the above dry resin (0.1918 mmol) in 5 mL of anhydrous tetrahydrofuran was added 246 mg (1.918 mmol) of potassium trimethylsilanolate (90%).

- 5 After the mixture was shaken at rt for 16 h, the resin was washed with THF (3 x 10 mL) and CH₂Cl₂/MeOH (1:1, 6 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 480 [M+H]⁺.

- 10 To a mixture of the above dry resin (0.1918 mmol) in 10.7 mL of anhydrous tetrahydrofuran was added 359 mg (1.918 mmol) of (R)-3-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (Kucznierz, et. al. *J. Med. Chem.* **1998**, *41*, 4983-4994) and 503 mg (1.918 mmol) of triphenylphosphine. After the mixture was cooled to -78 °C, 378 µL (1.918 mmol) of diisopropyl azodicarboxylate was added to the cold mixture. The resulting
- 15 mixture was kept at -70 °C for 30 min while shaking. The mixture was then allowed to warm to 0 °C over 1 h and shaken at rt for 16 h. The resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. The dry resin was treated with 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2h. After the cleavage solution was collected,
- 20 the resin was treated with another 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H₂O (0.1% trifluoroacetic acid) and B = CH₃CN (0.1% trifluoroacetic acid) pumped at 25
- 25 mL/min, to produce benzo[b]thiophene-2-carboxylic acid [(*S*)-3-methyl-1-((*S*)-1-(2-[4-((*S*)-pyrrolidin-3-yloxy)-phenyl]-ethyl)-pyrrolidin-3-ylcarbamoyl)-butyl]-amide as a bis-trifluoroacetic acid salt (clear oil, 22 mg, 21% over 8 steps): MS (ESI) 549 [M+H]⁺.



Compounds derived from Scheme 1:

Example	R1	R2	X	R3	R4	MS (ES+) m/e
97	isobutyl	benzothiophen-2-yl	4-oxy	H	piperidin-4-yl	563 (M+H)
98	isobutyl	benzothiophen-2-yl	4-oxy	3-fluoro	piperidin-4-yl	581 (M+H)
99	isobutyl	benzothiophen-2-yl	4-oxy	3-chloro	piperidin-4-yl	597 (M+H)
100	isobutyl	benzothiophen-2-yl	4-oxy	3-bromo	piperidin-4-yl	641 (M+H)
101	isobutyl	benzothiophen-2-yl	4-oxy	3-methoxy	piperidin-4-yl	593 (M+H)
102	isobutyl	benzothiophen-2-yl	3-oxy	H	piperidin-4-yl	563 (M+H)
103	isobutyl	benzothiophen-2-yl	3-oxy	4-methoxy	piperidin-4-yl	593 (M+H)
104	isobutyl	benzothiophen-2-yl	4-oxy	3-fluoro	pyrrolidin-3(S)-yl	567 (M+H)
105	isobutyl	benzothiophen-2-yl	4-oxy	3-chloro	pyrrolidin-3(S)-yl	583 (M+H)
106	isobutyl	benzothiophen-2-yl	4-oxy	3-bromo	pyrrolidin-3(S)-yl	627 (M+H)
107	isobutyl	benzothiophen-2-yl	4-oxy	3-methoxy	pyrrolidin-3(S)-yl	579 (M+H)
108	isobutyl	benzothiophen-2-yl	4-oxy	3-nitro	pyrrolidin-3(S)-yl	594 (M+H)
109	isobutyl	benzothiophen-2-yl	3-oxy	H	pyrrolidin-3(S)-yl	549 (M+H)
110	isobutyl	benzothiophen-2-yl	3-oxy	4-methoxy	pyrrolidin-3(S)-yl	579 (M+H)
111	isobutyl	benzothiophen-2-yl	4-oxy	H	<i>cis</i> -4-aminocyclohexyl	577 (M+H)
112	isobutyl	benzothiophen-2-yl	3-oxy	H	<i>cis</i> -4-aminocyclohexyl	577 (M+H)
113	isobutyl	benzothiophen-2-yl	4-oxy	3-fluoro	pyrrolidin-3(R)-yl	567 (M+H)
114	isobutyl	benzothiophen-2-yl	4-oxy	3-chloro	pyrrolidin-3(R)-yl	583 (M+H)
115	isobutyl	benzothiophen-2-yl	4-oxy	3-bromo	pyrrolidin-3(R)-yl	627 (M+H)
116	isobutyl	benzothiophen-2-yl	4-oxy	3-methoxy	pyrrolidin-3(R)-yl	579 (M+H)
117	isobutyl	benzothiophen-2-yl	4-oxy	3-nitro	pyrrolidin-3(R)-yl	594 (M+H)
118	isobutyl	benzothiophen-2-yl	3-oxy	4-methoxy	pyrrolidin-3(R)-yl	579 (M+H)

Example 119

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

5	<u>Tablets/Ingredients</u>	<u>Per Tablet</u>
	1.Active ingredient (Cpd of Form. I)	40 mg
	2. Corn Starch	20 mg
	3.Alginic acid	20 mg
10	4.Sodium Alginate	20 mg
	5.Mg stearate	<u>1.3 mg</u> 2.3 mg

Procedure for tablets:

- 15 Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.
 Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.
 Step 3 The wet mass is converted to granules by passing it through an oscillating granulator
 20 using a No. 8 mesh (2.38 mm) screen.
 Step 4 The wet granules are then dried in an oven at 140°F (60°C) until dry.
 Step 5 The dry granules are lubricated with ingredient No. 5.
 Step 6 The lubricated granules are compressed on a suitable tablet press.

25 Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Parenteral Formulation

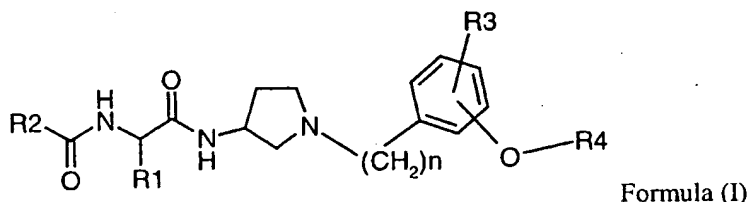
- 30 A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

35

- The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other
- 5 publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound of Formula (I):



5 wherein:

R₁ is isobutyl, isopropyl, benzyl, carbamoylmethyl;

R₂ is methyl, phenyl, naphthyl, indolyl, benzimidazolyl, quinoliny, furanyl, thiophenyl, pyridyl, benzofuranyl, or benzothiophenyl, substituted or unsubstituted by one or two halogen, methyl, methoxy, or methylenedioxy groups;

10 R₃ is hydrogen, halogen, methyl, methoxy, nitro, or 2,3-(1,3-butadien-1,4-yl);

R₄ is 3-dimethylaminopropyl, 2-(pyrrolidin-1-yl)ethyl, 2-(1-morpholino)ethyl, 2-(N-methyl anilino)ethyl, 2-(1-piperazinyl)ethyl, 2-(1-pyrrolidinonyl) ethyl, (1-methylpyrrolidin-2(S)-yl)methyl, 1-methylpyrrolidin-3(±)-yl, 1-benzylpiperidin-4-yl, (6-methylpyrid-2-yl)methyl, 3-dimethylamino benzyl, 2(S)-(aminocarbonyl) pyrrolidin-4(S)-yl, pyrrolidin-3(S)-yl,

15 piperidin-4-yl, pyrrolidin-3(R)-yl, or *cis*-4-aminocyclohexyl; and

n is 1 or 2;

or a pharmacologically acceptable salt thereof.

2. A compound of Claim 1 wherein R₁ is isobutyl, isopropyl, or benzyl; R₂ is
20 phenyl, naphthyl, furanyl, thiophenyl, benzofuranyl, or benzothiophenyl, substituted or unsubstituted with one or two halogen, methyl, methoxy, or methylenedioxy groups; R₃ is hydrogen, halogen, methyl, or methoxy; R₄ is 3-dimethylaminopropyl, 2-(1-piperazinyl)ethyl, 2-(1-pyrrolidinonyl) ethyl, 1-methylpyrrolidin-3(±)-yl, 1-benzylpiperidin-4-yl, pyrrolidin-3(S)-yl, piperidin-4-yl, or pyrrolidin-3(R)-yl; and n is 1.

25

3. A compound of Claim 1 chosen from:

Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-iodo-3-(2-piperazin-1-yl-ethoxy)-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide;

30 Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[3-(3-dimethylamino-propoxy)-4-iodo-benzyl]-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl)-amide;

- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-(3-dimethylamino-propoxy)-benzyl]-pyrrolidin-3-ylcarbomoyl)-3-methyl-butyl)-amide;
- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-(1-benzyl-piperidin-4-yloxy)-3-chloro-benzyl]-pyrrolidin-3-ylcarbomoyl)-3-methyl-butyl)-amide;
- 5 Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[3-bromo-4-(3-dimethylamino-propoxy)-benzyl]-pyrrolidin-3-ylcarbomoyl)-3-methyl-butyl)-amide;
- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[3-bromo-4-(1-methyl-pyrrolidin-3-yloxy)-benzyl]-pyrrolidin-3-ylcarbomoyl)-3-methyl-butyl)-amide;
- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[4-(1-benzyl-piperidin-4-yloxy)-3-bromo-benzyl]-pyrrolidin-3-ylcarbomoyl)-3-methyl-butyl)-amide;
- 10 Benzofuran-2-carboxylic acid ((S)-1-((S)-1-[4-(3-dimethylamino-propoxy)-benzyl]-pyrrolidin-3-ylcarbomoyl)-3-methyl-butyl)-amide;
- Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[3-bromo-4-(piperidin-4-yloxy)-benzyl]-pyrrolidin-3-ylcarbomoyl)-3-methyl-butyl)-amide; and
- 15 Benzo[b]thiophene-2-carboxylic acid ((S)-1-((S)-1-[3-bromo-4-((R)-pyrrolidin-3-yloxy)-benzyl]-pyrrolidin-3-ylcarbomoyl)-3-methyl-butyl)-amide.

4. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

5. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 1.

6. A method according to Claim 5 wherein the disease is congestive heart failure, stroke, ischemic heart disease, angina, myocardial ischemia, cardiac arrhythmias, essential hypertension, pulmonary hypertension, COPD, restenosis, asthma, neurogenic inflammation metabolic vasculopathies, addiction, schizophrenia, impulsivity, anxiety, stress, depression, neuromuscular function, or diabetes.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/34546

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, WEST, EAST, MEDLINE, BIOSIS

search terms: urotensin?, congestive(L)heart?, asthma?, restinos?, inflamma?, angina?, stroke?, diabet?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,680,283 A (VEBER et al.) 14 July 1987, see entire document.	1-6
X	WO 98/50534 A1 (SMITHKLINE BEECHAM CORPORATION) 12 November 1998, see entire document.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

22 FEBRUARY 2001

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/34546

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

A61K 31/34, 31/341, 31/38, 31/381, 31/44, 31/4427, 31/4439, 31/445, 31/454, 31/47, 31/4709, 31/495, 31/496, 31/535, 31/5375, 31/5377; C07D 207/09, 207/10, 207/12, 207/14, 207/30, 207/32, 207/333, 207/335; 209/12, 209/14; 213/02, 213/04, 213/24, 213/28, 213/44, 213/46, 213/50; 215/02, 215/12, 215/14, 215/38; 307/38, 307/42, 307/46, 307/52; 401/12; 403/12; 405/12; 409/12; 413/10, 413/12

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/235.5, 254.01, 314, 326, 327, 331, 337, 343, 387, 396, 397, 414, 419, 422, 423, 424, 444, 461; 544/141, 372; 546/112, 169, 208, 279.1; 548/306.1, 492, 495, 523, 526, 537, 540, 541, 543, 557

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/235.5, 254.01, 314, 326, 327, 331, 337, 343, 387, 396, 397, 414, 419, 422, 423, 424, 444, 461; 544/141, 372; 546/112, 169, 208, 279.1; 548/306.1, 492, 495, 523, 526, 537, 540, 541, 543, 557